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FOREWORD

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The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

This report has been reviewed and is approved.

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Commander

ABSTRACT

The kinetics of recuperation following initial doses of 470 rads of 55 Mev protons and 350 rads of Co^{60} γ radiation were investigated by means of the paired-dose method. By using semilog plots, recovery half-times of 4.85 $\pm$ .85 days and 2.02 $\pm$ .45 days were found after initial doses of the protons and Co^{60} γ radiation, respectively.

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I. INTRODUCTION

Since space travel will place man in a position to be irradiated with protons, a most important consideration concerns the characteristics of recovery from the injury produced by the protons. This communication gives the results of experiments in which the kinetics of recuperation after 55 Mev protons and Co^{60} γ irradiation were studied by the paired-dose method. Throughout the literature, the terms "repair" and "recovery" are given specialized meanings. The term "recuperation" (after Kallman and Silini (1)) will be used to indicate the improvement of the radiation-induced injury with time.

II. EXPERIMENTAL METHODS AND MATERIALS

Protons

The Oak Ridge Isochronous Cyclotron (ORIC) was used as a source of the protons. Mice were irradiated in groups of 3 with doses of 470 rads of 55 Mev protons delivered at 470 rads/min.; they were held in aluminum mesh cylinders and rotated at a rate of 10 r.p.m. during exposure. The experimental arrangement and the beam characteristics have already been described (2, 3).

Co^{60} γ irradiations

The USAF School of Aerospace Medicine Cobalt Irradiation Facility was used for the exposures. The mice were irradiated in groups of 12; the beam characteristics and the dosimetry have already been described (4).

Animals and experimental design

A total of 1,352 adult, female, white Swiss Webster mice was used; they were obtained in a single shipment from a single supplier (Simonson Laboratories, White Bear Lake, Minn.) when they were approximately 8 weeks old. Immediately after arrival, the mice were assigned to plastic cages (6 mice to each cage) by a random number table and subsequently maintained in the animal quarters until time for exposure. The details of the animal care have already been described (4).

Just prior to irradiation the mice were divided into four basic groups by use of a random number table. Groups I and II were made up of 576 mice each. Those of group I were given single doses of 350 rads of Co^{60} γ radiation delivered at 350 rads/min. while the mice of group II received 470 rads of 55 Mev protons given at 470 rads/min. The original plan was to deliver initial doses of 350 rads of the 55 Mev protons to parallel the Co^{60} exposures. After the irradiations (both protons and Co^{60}) had been completed, however, an error in proton dosimetry was detected. The gas pressure within the ion chamber was found to be excessively low. This meant that a larger dose was required to produce a unit amount of ionization (as determined during the first calibration at the correct gas pressure) (2). Recalibration at the correct gas pressure indicated that the dose delivered during a 1-minute exposure was 470 rads. Although there had been an error in absolute dosimetry, the relative dosimetry was not affected; the cyclotron beam current remained very stable during all of the irradiations. After irradiation, these large groups were further subdivided by a random number table into groups

TABLE I

Experimental results

Days after irradiation	350 rads Co^{60} γ radiation (initial dose)			450 rads 55 Mev protons (initial dose)		
	Number of animals	$LD_{50/30}$ on day	Injury (rads)	Number of animals	$LD_{50/30}$ on day	Injury* (rads)
0†	144	735 ± 18‡	—	—	—	—
1	144	555 ± 19	180 ± 26	144	308 ± 18	427 ± 25
2	144	582 ± 20	153 ± 27	144	256 ± 26	479 ± 32
4	144	607 ± 18	128 ± 25	144	358 ± 28	377 ± 33
8	144	753 ± 31	−18 ± 36	144	565 ± 16	155 ± 24

*In this context, injury is the difference between the single dose $LD_{50/30}$ for Co^{60} γ radiation, 735 rads, and the $LD_{50/30}$ on a given day after the initial exposure.

†Only single doses of Co^{60} were given to the mice to determine the $LD_{50/30}$ of the normal population.

‡S.E.

of 144 mice each which were given challenging doses of Co^{60} γ radiation on 1, 2, 4, or 8 days after the initial dose. The specific time at which a given group would receive the challenging doses was decided by a random number table.

Each group of 144 animals was divided by a random number table into six subgroups of 24 mice each which were given single-spaced doses of Co^{60} γ radiation delivered at 350 rads/min. for estimation of $LD_{50/30}$'s. Therefore, at each time period after the initial doses, $LD_{50/30}$'s were estimated from 144 exposed mice (6 doses × 24 mice/dose). It should be noted that the animals of both group I and group II were given challenging doses of Co^{60} γ radiation; the only proton doses were the initial doses to group II.

The 144 mice of group III were subdivided by a random number table into six groups of 24 mice each and given spaced single doses of Co^{60} γ radiation; these mice served as irradiated controls. The 200 mice of group IV were nonirradiated controls. Of these, 120 were sham-irradiated while the others were left undisturbed in the animal quarters.

During the 60-day postirradiation period, the animals were observed daily (including Sundays and holidays) for dead animals.

III. RESULTS AND DISCUSSION

The $LD_{50/30}$'s were calculated from the 30-day cumulative mortality data by probit analysis (5); these values are given in table I. After the initial exposure with either the Co^{60} γ radiation or the 55 Mev protons, there was a progressive increase in the $LD_{50/30}$ during the 8-day recuperation period. While a rising $LD_{50/30}$ indicates a lessening of the injury induced by the initial dose, the kinetics of the recuperation process are more satisfactorily studied by considering the differences between the irradiated control group and the group which received the initial exposures. The rationale behind this method has been described in detail by Sacher (6) and by Kallman and Silini (1).

With this convention, the difference between the $LD_{50/30}$'s may be considered to represent the amount of residual injury remaining at the time that the challenging exposures were given; the injury would be in units of rads of the challenging radiation. The amounts of residual injury calculated by this means are given in table I.

Figure 1 shows these results plotted on a semilog coordinate system. The curves were fitted by the method of least squares. The

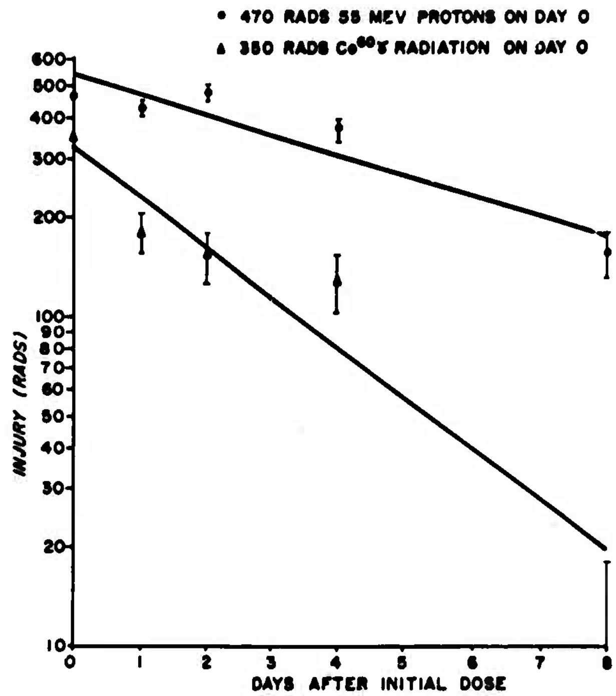

FIGURE 1

Semilog plot of injury as a function of time after the initial dose. Since logarithms are not defined for negative numbers, the —18 rads remaining at 8 days after 350 rads of Co^{60} γ radiation could not be plotted. The vertical bars indicate standard errors. The initial dose is plotted as the "zero-time" injury.

curve for the animals given an initial exposure of 470 rads of 55 Mev protons is given by:

$$Y_p = 548\ (\pm\ 206)\ \exp\ (-.1430 \pm (.0288)) \qquad (1)$$

where Y_p is the amount of residual injury (in rads) remaining at t days after the initial dose; the intercept and slope standard errors are enclosed in the parentheses. The correlation coefficient is —.944. Therefore, the recuperation half-time given by this curve is 4.85 ± .85 (S.E.) days.

The curve for the mice given an initial dose of 350 rads of Co^{60} γ radiation is given by:

$$Y_c = 327\ (\pm\ 179)\ \exp\ (-.3422 \pm (.0490)) \qquad (2)$$

The correlation coefficient is —.9707. The recuperation half-time given by this curve is 2.02 ± .45 (S.E.) days. Comparison of the slopes of these curves by means of Student's t-test indicates a significant ($P < .01$) difference.

A great deal has been written about the value (and limitation) of the paired-dose technic for studying the kinetics of recuperation after irradiation (1, 6-11). While this technic represents at best a gross view of the recuperative process, it has been widely applied over the last two decades. The purpose of the present study was neither to add new dimensions to the paired-dose technic nor to broaden the controversy. Rather, the primary goal has been simply to compare the recuperation curves after proton and Co^{60} γ irradiation.

The use of Co^{60} γ radiation challenging exposures to evaluate the effects of another type of radiation, such as 55 Mev protons, has been used, in principle, by other workers for several years. The basic concept is that the amount of injury remaining after proton irradiation will manifest itself by a lowering of the $LD_{50/30}$ in proportion to an amount equivalent to a given number of rads of the challenging (Co^{60} γ) radiation.

The semilog plots shown in figure 1 indicate that although the recuperation half-times are significantly different (on statistical grounds) after 55 Mev protons and Co^{60} γ radiation, the results are comparable with the findings of a number of other studies (7). This interpretation assumes that recuperation following irradiation progresses in an exponential manner (5). Since a 40% larger initial dose of protons was used, this change may be a consequence of this larger dose. The results, therefore, would suggest that there does not appear to be any gross difference in the manner in which injury after 55 Mev proton irradiation is repaired as compared with the Co^{60} γ radiation.

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